Guidance for Industry

Non-Penicillin Beta-Lactam Risk Assessment: A CGMP Framework

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2011
Current Good Manufacturing Practices (CGMPs)

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I. INTRODUCTION

This guidance describes the importance of implementing appropriate steps during the manufacturing process to prevent cross-contamination of finished pharmaceuticals and active pharmaceutical ingredients (APIs) with non-penicillin beta-lactam antibiotics. This guidance also provides information regarding the relative health risk of, and the potential for, cross-reactivity in the classes of sensitizing beta-lactams (penicillins and non-penicillin beta-lactams). This guidance is intended to assist manufacturers in assessing whether separate facilities should be used based on the relative health risk of cross-reactivity.

Drug cross-contamination is the contamination of one drug with one or more different drugs. Penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people. Accordingly, developing strategies to prevent cross-contamination of other drugs with penicillin is a key element of manufacturing penicillin. Non-penicillin beta-lactam drugs may also be sensitizing agents, and cross-contamination with non-penicillin beta-lactam drugs can initiate drug-induced hypersensitivity reactions, including anaphylaxis, an allergic reaction that may be a life-threatening event. As with penicillin, a critical aspect of manufacturing non-penicillin beta-lactam drugs is preventing cross-contamination to reduce the potential for drug-induced, life-threatening allergic reactions.

The information in this guidance is intended for manufacturers of finished pharmaceuticals and APIs, including repackagers. Other establishments that handle drugs, such as pharmacy compounders, may find this information useful.

[1] This guidance was developed by the Office of Compliance, Division of Manufacturing and Product Quality, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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II. BACKGROUND

Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) requires that, with few exceptions, all drugs be manufactured in compliance with current good manufacturing practices (CGMPs). Drugs that are not in compliance with CGMPs are considered to be adulterated. Furthermore, finished pharmaceuticals are required to comply with the CGMP regulations at 21 CFR parts 210 and 211.

Several CGMP regulations directly address facility and equipment controls and cleaning. For example, § 211.42(c) requires building and facility controls in general to prevent cross-contamination of drug products. Specifically, the regulation states, "[t]here shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups" during manufacturing, processing, packaging, storage, and holding processes.

With respect to penicillin, § 211.42(d) requires that "[o]perations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use." However, FDA has clarified that separate buildings may not be necessary, provided that the section of the manufacturing facility dedicated to manufacturing penicillin is structurally isolated (i.e., completely and comprehensively separated) from the areas of the facility in which non-penicillin products are manufactured.[2] Under § 211.46(d), manufacturers must completely separate air handling systems for penicillin from those used for other drugs for human use. Similarly, § 211.176 requires manufacturers to test non-penicillin drug products for penicillin where the possibility of exposure to cross-contamination exists, and prohibits manufacturers from marketing such products if detectable levels of penicillin are found.[3]

Although FDA has not issued CGMP regulations specific to APIs, the Agency has provided guidance to API manufacturers in the guidance for industry, ICH[4] Q7, *Good Manufacturing*

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[2] Preamble to the final rule, "Current Good Manufacturing Practice, Processing, Packing, or Holding," published in the FEDERAL REGISTER of September 29, 1978 (43 FR 45014 at 45038).

[3] See "A Review of Procedures for the Detection of Residual Penicillins in Drugs" (Appendix I, *Procedures for Detecting and Measuring Penicillin Contamination in Drugs*, FDA By-Lines No. 8 (November 1977)), available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM095812.pdf.

[4] International Conference on Harmonization.

Practice Guidance for Active Pharmaceutical Ingredients (ICH Q7 guidance).[5] Because some APIs are sensitizing compounds that may cause anaphylactic shock, preventing cross-contamination in APIs is as important as preventing cross-contamination in finished products. The ICH Q7 guidance recommends using dedicated production areas, which can include facilities, air handling equipment, and/or processing equipment, in the production of highly sensitizing materials, such as penicillins and cephalosporins.[6]

Beta-lactam antibiotics share a basic chemical structure that includes a three-carbon, one-nitrogen cyclic amine structure known as the beta-lactam ring. The side chain associated with the beta-lactam ring is a variable group attached to the core structure by a peptide bond. The side chain variability contributes to antibacterial activity.

As of the date of this publication, FDA has approved over 34 beta-lactam compounds as active ingredients in drugs for human use.[7] Beta-lactam antibiotics include the following five classes:

- penicillins (e.g., ampicillin, oxacillin)
- cephalosporins (e.g., cephalexin, cefaclor)
- penems (e.g., imipenem, meropenem)
- carbacephems (e.g., loracarbef)
- monobactams (e.g., aztreonam)[8]

The penicillins, cephalosporins, penems, and carbacephems share a characteristic bicyclic core structure, which is believed to initiate allergic reactions. The monobactam aztreonam has a unique monocyclic beta-lactam nucleus and rarely cross-reacts with penicillins and cephalosporins.[9] Aztreonam and ceftazidime have a common side chain, and cross-reactivity between aztreonam and ceftazidime has been reported.[10]

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[5] We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the Guidance Page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[6] See section IV.D Containment (4.4) of the ICH Q7 guidance.

[7] Approved beta-lactam antibiotics are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, generally known as the *Orange Book* (available on the Internet at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm). The Orange Book is searchable by active ingredient and updated as newer drug products are added.

[8] Yao, JDC, and RC Moellering, Jr., Antibacterial agents, in *Manual of Clinical Microbiology*, 9th edition, edited by PR Murray et al., Washington D.C., ASM Press, 2007.

[9] American Academy of Allergy, Asthma, and Immunology, 1999, Disease management of drug hypersensitivity: a practice parameter, Ann Allergy Asthma Immunol, 83(supp): S665-S700.

[10] Perez Pimiento, A, M Gomez Martinez, A Minguez Mena, A Trampal Gonzalez, S de Paz Arranz, and M Rodriguez Mosquera, 1998, Aztreonam and ceftazidime: evidence of in vivo cross-allergenicity, Allergy, 53:624-625.

Beta-lactam antibiotics inhibit bacterial cell wall synthesis. Many bacteria produce beta-lactamases, which are enzymes that degrade and inactivate beta-lactam antibiotics. Beta-lactam compounds such as clavulanic acid, tazobactam, and sulbactam have weak antibacterial activity but are irreversible inhibitors of many beta-lactamases; they are used in combination with specific beta-lactam agents to preserve antibacterial activity.

Allergic reactions associated with penicillins and non-penicillin beta-lactam antibiotics range from rashes to life-threatening anaphylaxis. Immunoglobulin E (IgE) antibodies mediate the immediate hypersensitivity reactions that are responsible for the symptoms of hay fever, asthma, hives, and anaphylactic shock. IgE-mediated hypersensitivity reactions are of primary concern because they may be associated with significant morbidity and mortality. There is evidence that patients with a history of hypersensitivity to penicillin may also experience IgE-mediated reactions to cephalosporins and penems.[11] Cross-reactivity (cross-sensitivity) between beta-lactam products has been and continues to be a major concern in the manufacture of drugs.

All non-penicillin beta-lactam antibiotics also have the potential to sensitize individuals, and subsequent exposure to penicillin may result in severe allergic reactions in some patients. Although the frequency of hypersensitivity reactions due to cross-reactivity between beta-lactam classes can be lower than the risk within a class,[12] the hazard posed is present[13] and potentially life-threatening. The potential health hazard of non-penicillin beta-lactam drugs is therefore similar to that of penicillins. Further similarities between non-penicillin beta-lactam antibiotics and penicillins are as follows:

- It is difficult to define the minimal dose below which allergic responses are unlikely to occur in humans. [14]
- There is a lack of suitable animal or receptor testing models that are predictive of human sensitivity. [15]
- The threshold dose at which allergenic response could occur is extremely low and

[11] Saxon, A, DC Adelman, A Patel, R Hajdu, and GB Calandra, 1988, Imipenem cross-reactivity with penicillin in humans, J Allergy Clin Immunol, 82:213-217; Saxon, A, GN Beall, AS Rohr, and DC Adelman, 1987, Immediate hypersensitivity reactions to beta-lactam antibiotics, Ann Intern Med, 107(2):204-215; Prescott, Jr., WA, DD DePestel, JJ Ellis, and RE Regal, 2004, Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy, Clin Infect Dis, 38:1102-1107.

[12] Salkind, AR, PG Cuddy, and JW Foxworth, 2001, Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy, JAMA, 285:2498-2505.

[13] Khan, D. and R Solensky , 2010, Drug Allergy, J Allergy Clin Immunol. 125(2): S131.

[14] Dayan, AD, 1993, Allergy to antimicrobial residues in food: assessment of the risk to man, Vet Microbiol, 35:213-226; Blanca, M, J Garcia, JM Vega, A Miranda, MJ Carmona et al., 1996, Anaphylaxis to penicillins after non-therapeutic exposure: an immunological investigation, Clin Exp Allergy, 26:335-340.

[15] Olson, H, G Betton, D Robinson, K Thomas, A Monro et al., 2000, Concordance of the toxicity of pharmaceuticals in humans and in animals, Regul Toxicol Pharmacol, 32:56-67.

difficult to detect with current analytical methods.[16]

Some beta-lactam intermediate compounds and derivatives possess sensitization and cross–reactivity properties. Beta-lactam chemical manufacturing processes including, but not limited to, fermentation and synthesis may create beta-lactam intermediates or derivatives with unknown health consequences. Therefore, the health risk of sensitization and cross-reaction is difficult to predetermine for beta-lactam intermediates, and is not always well-defined.

Beta-lactam intermediate compounds are usually API precursor materials that undergo molecular change or purification before use in the manufacture of beta-lactam antibiotic APIs. As a result of these changes, the intermediate compounds may develop antigenic characteristics that can produce allergic reactions. For example, 6-aminopenicillanic acid (6-APA) serves as the intermediate for the formation of all synthetic penicillins that are formed by attaching various side chains. The structure of 6-APA includes unbroken beta-lactam and thiazolidine rings. The beta-lactam ring is relatively unstable, and it commonly breaks open. In the case of 6-APA, this breakage leads to the formation of a penicilloyl moiety, which is also known as the major antigenic determinant of penicillin. This moiety is thought to be a common cause of penicillin urticarial reaction.[17] Degradation of 6-APA can also result in the formation of minor antigenic determinants, including penicilloic acids, penaldic acid, and penicillamine. Anaphylactic reactions to penicillins are usually due to IgE antibodies to minor determinants. Therefore, although 6-APA is not a true antibiotic, it still carries with it a potential to induce allergenicity.

Derivatives are unintended by-products that occur during the manufacturing process (i.e., an impurity or degradant) which could have sensitizing properties. Similar to intermediates, beta-lactam derivatives may also develop antigenic properties that can produce allergic reactions.

Beta-lactam antibiotics are similar to one another in many ways, but they may differ in pharmacokinetics, antibacterial activity, and potential to cause serious allergic reactions. Because allergy testing methods have not been well-validated,[18] it is clinically difficult to determine the occurrence and rate of cross-reactivity between beta-lactam antibiotics in humans. Therefore, undiagnosed or underreported cases of cross-reactivity likely exist. Some beta-lactam antibiotics have negligible potential for cross-reactivity with beta-lactams of other classes, whereas other beta-lactam compounds may exhibit sensitizing activity as derivatives before the incorporation of side chains that confer antibacterial activity.

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[16] Perez Pimiento, A, M Gomez Martinez, A Minguez Mena, A Trampal Gonzalez, S de Paz Arranz, and M Rodriguez Mosquera, 1998, Aztreonam and ceftazidime: evidence of in vivo cross-allergenicity, Allergy, 53:624-625; Shepard, GM, 1991, Allergy to B-lactam antibiotics, Immunol Allergy Clin North Am, 11(3):611-633.

[17] Middleton Principle of Allergy and Immunology: Principles and Practice, 2009 edition, chapter 68: Drug Allergy, electronic book version, at the sentence above Figure 68.2.

[18] Bernstein, IL, JT Li, DI Bernstein, et al., 2008, Allergy diagnostic testing: an updated practice parameter, Ann Allergy Asthma Immunol, 100:S1-S148.

III. RECOMMENDATIONS

Because of the health risks associated with cross-reactivity (cross-sensitivity) of beta-lactams, non-beta-lactam manufacturers should assess and establish stringent controls (including appropriate facility design provisions assuring separation) to prevent cross-contamination. Just as FDA considers the separation of production facilities for penicillins to be current good manufacturing practice, FDA expects manufacturers to treat sensitizing non-penicillin beta-lactam-based products similarly. Specifically, FDA recommends that manufacturers establish appropriate separation and control systems designed to prevent the following types of cross-contamination:

- Non-penicillin beta-lactam contamination in a non-beta-lactam product (e.g., cefaclor in aspirin)
- Non-penicillin beta-lactam contamination in another non-penicillin beta-lactam (e.g., cephalexin in imipenem)

As with penicillin, the section of a facility dedicated to manufacturing a sensitizing non-penicillin beta-lactam should be structurally isolated (i.e., completely and comprehensively separated) from areas in the facility in which other products are manufactured. This control applies to each of the five classes of sensitizing beta-lactams; the area in which any class of sensitizing beta-lactam is manufactured should be separated from areas in which any other products are manufactured, including any other class of sensitizing beta-lactam or any other non-beta-lactam product. Manufacturing that is restricted to a specific class of beta-lactam compound (e.g., the cephalosporin family of products) would generally not mandate separate facilities and air handling systems, and could permit production campaigning and cleaning as sufficient control.